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FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH, LIFESCI' ENTERED AT 16:13:11 ON 18 JUL 2005

L1 2322 S FIBRIN(3A)GEL
L2 3651390 S NUCLEIC(W)ACID OR POLYNUCLEOTIDE OR DNA
L3 69 S L1 AND L2
L4 1889541 S TRANSFORM? OR TRANSFECT?
L5 24 S L3 AND L4
L6 13 DUP REM L5 (11 DUPLICATES REMOVED)

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L6 ANSWER 1 OF 13 MEDLINE on STN
AU Schek Rachel Maddox; Hollister Scott J; Krebsbach Paul H
TI Delivery and protection of adenoviruses using biocompatible hydrogels for localized gene therapy.
SO Molecular therapy : journal of the American Society of Gene Therapy, (2004 Jan) 9 (1) 130-8.
Journal code: 100890581. ISSN: 1525-0016.
AB Localized gene delivery for repair of bone defects requires appropriate carriers for the gene therapy vectors. The objective of this study was to determine if hydrogels can control temporal and spatial delivery of adenovirus for localized gene therapy. Adenovirus expressing beta-galactosidase was suspended in liquid or **fibrin** or collagen **gels** of varied concentrations and incubated prior to testing its bioactivity. The bioactivity of the virus was determined by exposing fibroblasts to the medium, the gels, or the elution medium from the gels. Bioactivity of adenovirus suspended in medium or collagen decreased to half-maximal activity after 15 h of incubation. In contrast, virus suspended in fibrin exhibited a threefold extension of bioactivity and did not reach half-maximal activity for 45 h. Bioactivity of adenovirus in hydrogels was determined to be a function of the gel concentration. In vivo experiments involved intramuscular implantation of BMP-7-expressing adenovirus in collagen, fibrin, or liquid in nude mice for 1, 2, or 4 weeks. Bone formation was observed only after 4 weeks, with bone formation occurring in 80% of muscles implanted with fibrin or collagen and 50% of muscles implanted with liquid. **Fibrin gel** also led to significantly larger ossicles, indicating that fibrin may offer protection from loss of infectivity both in vivo and in vitro. These results demonstrated that hydrogels may be used as carriers to control delivery of the virus and resultant tissue regeneration.

L6 ANSWER 2 OF 13 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
AU Leali D; Belleri M; Urbinati C; Coltrini D; Oreste P; Zoppetti G; Ribatti D; Rusnati M; Presta M (Reprint)
TI Fibroblast growth factor-2 antagonist activity and angiostatic capacity of sulfated Escherichia coli K5 polysaccharide derivatives
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (12 OCT 2001) Vol. 276, No. 41, pp. 37900-37908.
ISSN: 0021-9258.
AB The angiogenic basic fibroblast growth factor (FGF2) interacts with tyrosine kinase receptors (FGFRs) and heparan sulfate proteoglycans (HSPGs) in endothelial cells. Here, we report the FGF2 antagonist and antiangiogenic activity of novel sulfated derivatives of the Escherichia coli K5 polysaccharide. K5 polysaccharide was chemically sulfated in N- and/or O-position after N-deacetylation. O-Sulfated and N,O-sulfated K5 derivatives with a low degree and a high degree of sulfation compete with heparin for binding to I-125-FGF2 with different potency. Accordingly, they abrogate the formation of the HSPG.FGF2.FGFR ternary complex, as

evidenced by their capacity to prevent FGF2-mediated cell-cell attachment of FGFR1-overexpressing HSPG-deficient Chinese hamster ovary (CHO) cells to wildtype CHO cells. They also inhibited I-125-FGF2 binding to FGFR1-overexpressing HSPG-bearing CHO cells and adult bovine aortic endothelial cells. K5 derivatives also inhibited FGF2-mediated cell proliferation in endothelial GM 7373 cells and in human umbilical vein endothelial (HUVE) cells. In all these assays, the N-sulfated K5 derivative and unmodified K5 were poorly effective. Also, highly O-sulfated and N,O-sulfated K5 derivatives prevented the sprouting of FGF2-**transfected** endothelial FGF2-T-MAE cells in **fibrin gel** and spontaneous angiogenesis in vitro on Matrigel of FGF2-T-MAE and HUVE cells. Finally, the highly N,O-sulfated K5 derivative exerted a potent antiangiogenic activity on the chick embryo chorioallantoic membrane. These data demonstrate the possibility of generating FGF2 antagonists endowed with antiangiogenic activity by specific chemical sulfation of bacterial K5 polysaccharide. In particular, the highly N,O-sulfated K5 derivative may provide the basis for the design of novel angiostatic compounds.

L6 ANSWER 3 OF 13 MEDLINE on STN DUPLICATE 1
AU Dell'Era P; Belleri M; Stabile H; Massardi M L; Ribatti D; Presta M
TI Paracrine and autocrine effects of fibroblast growth factor-4 in endothelial cells.
SO Oncogene, (2001 May 10) 20 (21) 2655-63.
Journal code: 8711562. ISSN: 0950-9232.
AB Recombinant Fibroblast Growth Factor-4 (FGF4) and FGF2 induce extracellular signal-regulated kinase-1/2 activation and **DNA** synthesis in murine aortic endothelial (MAE) cells. These cells co-express the IIIc/Ig-3 loops and the novel glycosaminoglycan-modified IIIc/Ig-2 loops isoforms of FGF receptor-2 (FGFR2). The affinity of FGF4/FGFR2 interaction is 20-30 times lower than that of FGF2 and is enhanced by heparin. Overexpression of FGF2 or FGF4 cDNA in MAE cells results in a **transformed** phenotype and increased proliferative capacity, more evident for FGF2 than FGF4 **transfectants**. Both **transfectants** induce angiogenesis when applied on the top of the chick embryo chorioallantoic membrane. However, in contrast with FGF2-**transfected** cells, FGF4 **transfectants** show a limited capacity to growth under anchorage-independent conditions and lack the ability to invade 3D **fibrin gel** and to undergo morphogenesis in vitro. Also, they fail to induce hemangiomas when injected into the allantoic sac of the chick embryo. In conclusion, although exogenous FGF2 and FGF4 exert a similar response in MAE cells, significant differences are observed in the biological behavior of FGF4 versus FGF2 **transfectants**, indicating that the expression of the various members of the FGF family can differently affect the behavior of endothelial cells and, possibly, of other cell types, including tumor cells.

L6 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
IN Cederholm-Williams, Stewart A.
TI Fibrin sealant as a **transfection/transformation** vehicle for gene therapy
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
AB Provided, for example, is a method of **transforming** a cell comprising the steps of: applying a **transformation** effective amount of a **nucleic acid** to the cell; applying a **fibrin gel** to the cell so as to entrap a **transformation** effective amount of the **nucleic acid**; and **transforming** the cell with the **nucleic acid**. In one aspect, the **nucleic acid** is applied in admixt. with a fibrin or fibrinogen composition that forms the **fibrin gel**. The invention further relates to the uses

of fibrin sealant as a **transfection/transformation** vehicle for gene therapy.

L6 ANSWER 5 OF 13 MEDLINE on STN
AU Kang M A; Kim K Y; Seol J Y; Kim K C; Nam M J
TI The growth inhibition of hepatoma by gene transfer of antisense vascular endothelial growth factor.
SO journal of gene medicine, (2000 Jul-Aug) 2 (4) 289-96.
Journal code: 9815764. ISSN: 1099-498X.
AB BACKGROUND: Vascular endothelial growth factor (VEGF) is a potent mediator of angiogenesis and tumor growth in solid tumors. Therefore, to induce tumor regression, antiangiogenic agents to block VEGF need to be administered repeatedly. METHOD: We constructed the recombinant mammalian expression vector bearing an antisense-VEGF cDNA, pZeoVEGFa. We examined the effect of pZeoVEGFa on the growth of SK-HEP1 hepatoma cells, bovine capillary endothelial (BCE) cells, and tubule formation of BCE cells in **fibrin gel**. To evaluate the function of pZeoVEGFa in vivo, we implanted SK-HEP1 hepatoma cells subcutaneously into nude mice. RESULTS: In SK-HEP1 hepatoma cells, we showed that the synthesis of VEGF protein was suppressed by the stable and transient **transfection** of pZeoVEGFa. pZeoVEGFa inhibited the proliferation of BCE cells and significantly suppressed tubule formation of BCE cells. pZeoVEGFa inhibited a morphological change from a round shape to an elongated spindle shape in **fibrin gel**. When pZeoVEGFa was injected peritumorally by liposomes, tumor growth was inhibited. CONCLUSION: Endothelial cell proliferation, tubule formation and tumor growth may be diminished by down-regulation of endogenous VEGF expression in tumor cells or tissue. These findings indicate that the efficient down-regulation of the VEGF produced by tumor cells using antisense strategies has an antitumor effect. We suggest that VEGF-targeted antiangiogenic gene therapy could be an effective strategy to treat VEGF-producing tumors.

L6 ANSWER 6 OF 13 MEDLINE on STN
AU Fernandez Pujol B; Lucibello F C; Gehling U M; Lindemann K; Weidner N; Zuzarte M L; Adamkiewicz J; Elsasser H P; Muller R; Havemann K
TI Endothelial-like cells derived from human CD14 positive monocytes.
SO Differentiation; research in biological diversity, (2000 May) 65 (5) 287-300.
Journal code: 0401650. ISSN: 0301-4681.
AB In the present study, we show that endothelial-like cells (ELCs) can develop from human CD14-positive mononuclear cells (CD14 cells) in the presence of angiogenic growth factors. The CD14 cells became loosely adherent within 24 h of culture and subsequently underwent a distinct process of morphological **transformation** to caudated or oval cells with eccentric nuclei. After 1 week in culture the cells showed a clear expression of endothelial cell markers, including von Willebrand factor (vWF), CD144 (VE-cadherin), CD105 (endoglin), acetylated low-density lipoprotein (AC-LDL)-receptor, CD36 (thrombospondin receptor), FLT-1, which is vascular endothelial cell growth factor (VEGF) receptor-1, and, to a weaker extent, KDR (VEGF receptor-2). Furthermore, in these cells structures resembling Weibel-Palade bodies at different storage stages were identified by electron microscopy, and upon culturing on three-dimensional **fibrin gels** the cells build network-like structures. In addition, cell proliferation and vWF expression was stimulated by VEGF, and the endothelial cell adhesion molecules CD54 (ICAM-1), and CD106 (VCAM-1) became transiently inducible by tumor necrosis factor-alpha (TNF-alpha). In contrast, the dendritic markers CD1a, and CD83 were not expressed to any significant extent. The expression of CD68, CD80 (B7-1), CD86 (B7-2), HLA-DR and CD36 may also suggest that ELCs might be related to macrophages, sinus lining or microvascular endothelial cells. Taken together, our observations indicate that ELCs can differentiate from cells of the monocytic lineage,

suggesting a closer relationship between the monocyte/macrophage- and the endothelial cell systems than previously supposed.

L6 ANSWER 7 OF 13 MEDLINE on STN
AU Tan S T; Hasan Q; Velickovic M; Ruger B M; Davis R P; Davis P F
TI A novel in vitro human model of hemangioma.
SO Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc, (2000 Jan) 13 (1) 92-9.
Journal code: 8806605. ISSN: 0893-3952.
AB Hemangioma, the most common tumor of infancy, is characterized by a proliferation of capillary endothelial cells with multilamination of the basement membrane and accumulation of cellular elements, including mast cells. The initial rapid growth is followed by an inevitable but slow involution. The currently available therapies are empirical and unsatisfactory because what is known of the cellular and molecular basis of hemangioma development is rudimentary. Advances in the understanding of its programmed biologic behavior has been hampered by the lack of a valid human model. We report here a novel in vitro culture system that is a useful human model of hemangioma. A small fragment of hemangioma biopsy is embedded in **fibrin gel** in a well of culture plates and incubated in a serum-free, buffered-salt, minimal medium. A complex network of microvessels grows out from the tissue fragments. Biopsies taken from all three phases of hemangioma development were cultured successfully; proliferative phase samples developed microvessels in 1 to 4 days, involuting phase in 5 to 7 days, and involuted phase in 7 to 12 days. The relative growth rates of the microvessels in the culture of biopsies taken from different stages of hemangioma development reflect the growth patterns seen clinically. This model has been validated using histochemistry, immunohistochemistry, and reverse transcriptase-polymerase chain reaction. Comparison of the number, localization, and phenotype of endothelial and mast cells and the distribution of basement membrane constituents (type IV collagen, perlecan, and laminins) and growth factors (basic fibroblast growth factor, vascular endothelial growth factor, **transforming** growth factor-betas) in the biopsy and the tissue after culture shows that many of the characteristics of the original tissues were retained in culture. This in vitro human model of hemangioma overcomes some of the deficiencies associated with earlier models. It offers an opportunity for studying the precise cellular, biochemical, and molecular basis of hemangioma It may also help to elucidate the mechanisms of action of existing therapies and may lead to the identification of novel treatments for hemangioma.

L6 ANSWER 8 OF 13 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
AU Presta M (Reprint); Rusnati M; Belleri R; Morbidelli L; Ziche M; Ribatti D
TI Purine analogue 6-methylmercaptopurine riboside inhibits early and late phases of the angiogenesis process
SO CANCER RESEARCH, (15 MAY 1999) Vol. 59, No. 10, pp. 2417-2424.
ISSN: 0008-5472.
AB Angiogenesis has been identified as an important target for antineoplastic therapy. The use of purine analogue antimetabolites in combination chemotherapy of solid tumors has been proposed. To assess the possibility that selected purine analogues may affect tumor neovascularization, 6-methylmercaptopurine riboside (6-MMPR), 6-methylmercaptopurine, 2-aminopurine, and adenosine were evaluated for the capacity to inhibit angiogenesis in vitro and in vivo, 6-MMPR inhibited fibroblast growth factor-2 (FGF2)-induced proliferation and delayed the repair of mechanically wounded monolayer in endothelial GM 7373 cell cultures. 6-MMPR also inhibited the formation of solid sprouts within **fibrin gel** by FGF2-treated murine brain microvascular endothelial cells and the formation of capillary-like structures on Matrigel by murine aortic endothelial cells **transfected** with FGF2 cDNA, 6-MMPR affected FGF2-induced

intracellular signaling in murine aortic endothelial cells by inhibiting the phosphorylation of extracellular signal-regulated kinase-2, The other molecules were ineffective in all of the assays. In vivo, 6-MMPR inhibited vascularization in the chick embryo chorioallantoic membrane and prevented blood vessel formation induced by human endometrial adenocarcinoma specimens grafted onto the chorioallantoic membrane. Also, topical administration of 6-MMPR caused the regression of newly formed blood vessels in the rabbit cornea. Thus, 6-MMPR specifically inhibits both the early and the late phases of the angiogenesis process in vitro and exerts a potent anti-angiogenic activity in vivo. These results provide a new rationale for the use of selected purine analogues in combination therapy of solid cancer.

L6 ANSWER 9 OF 13 MEDLINE on STN DUPLICATE 2
AU Rio M D; Larcher F; Meana A; Segovia J; Alvarez A; Jorcano J
TI Nonviral transfer of genes to pig primary keratinocytes. Induction of angiogenesis by composite grafts of modified keratinocytes overexpressing VEGF driven by a keratin promoter.
SO Gene therapy, (1999 Oct) 6 (10) 1734-41.
Journal code: 9421525. ISSN: 0969-7128.
AB Cultured epithelial grafts have proven to be life-saving in the treatment of large skin losses. It has become apparent that one of the main difficulties of this technology is the overall poor take of the grafts as a consequence of severely damaged dermal beds. Skin substitutes providing both cultured keratinocytes, as an epidermal layer, and a dermal analogous offer a more suitable material for skin repair. Ex vivo transfer of stroma regeneration-promoting genes to keratinocytes appears to be an attractive strategy for improving the therapeutic action of these grafts. The use of epidermal-specific promoters as expression drivers of exogenous genes results in both high expression levels and stratum specificity, as shown in transgenic mice studies. Most current gene transfer protocols to primary keratinocytes involve transduction of epidermal cells with retroviral vectors. However, transfer of gene constructs harboring these long **DNA** fragment promoters cannot be achieved through viral transduction. In this paper, we describe a protocol consisting of lipid-mediated **transfection**, G418 selection and an enhanced green fluorescence protein (EGFP)-based enrichment step for obtaining high levels of transgene-expressing primary keratinocytes. Using this protocol, the cDNA for vascular endothelial growth factor (VEGF), a potent endothelial cell mitogen driven by the 5.2 kb bovine keratin K5 promoter, was stably **transfected** into pig primary keratinocytes. Genetically modified keratinocytes, expanded on live fibroblast-containing **fibrin gels** and transplanted to nude mice as a composite material, elicited a strong angiogenic response in the host stroma as determined by fresh tissue examination and CD31 immunostaining. Since the formation of a well-vascularized wound bed is a crucial step for permanent wound closure, the use of an 'angiogenic' composite material may improve wound bed preparation and coverage with cultured keratinocyte grafts.

L6 ANSWER 10 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AU Sabapathy, Kanaga T.; Pepper, Michael S.; Kiefer, Friedemann; Moehle-Steinlein, Uta; Tacchini-Cottier, Fabienne; Fetka, Ingrid; Breier, Georg; Risau, Werner; Carmeliet, Peter; Montesano, Roberto; Wagner, Erwin F. [Reprint author]
TI Polyoma middle T-induced vascular tumor formation: The role of the plasminogen activator/plasmin system.
SO Journal of Cell Biology, (1997) Vol. 137, No. 4, pp. 953-963.
CODEN: JCLBA3. ISSN: 0021-9525.
AB The middle T antigen of murine Polyomavirus (PymT) rapidly **transforms** endothelial cells, leading to the formation of vascular tumors in newborn mice. **Transformed** endothelial (End.) cell lines established from such tumors exhibit altered proteolytic activity as

a result of increased expression of urokinase-type plasminogen activator (uPA) and are capable of inducing vascular tumors efficiently when injected into adult mice. In this study we have used mice lacking components of the PA/plasmin system to analyze the role of this system in the **transformation** process and in tumor growth. We found that the proteolytic status of the host is not a critical determinant for PymT-induced vascular tumor formation. In addition, the lack of either uPA or tissue-type PA (tPA) activity is not limiting for the establishment and proliferation of End. cells in vitro, although the combined loss of both PA activities leads to a marked reduction in proliferation rates. Furthermore, the in vitro morphogenetic properties of mutant End. cells in **fibrin gels** could only be correlated with an altered proteolytic status in cells lacking both uPA and tPA. However, in contrast with tumors induced by PymT itself, the tumorigenic potential of mutant and wild-type End. cell lines was found to be highly dependent on the proteolytic status of both the tumor cells and the host. Thus, genetic alterations in the PA/plasmin system affect vascular tumor development, indicating that this system is a causal component in PymT-mediated oncogenesis.

L6 ANSWER 11 OF 13 MEDLINE on STN
AU Gualandris A; Rusnati M; Belleri M; Nelli E E; Bastaki M; Molinari-Tosatti M P; Bonardi F; Parolini S; Albini A; Morbidelli L; Ziche M; Corallini A; Possati L; Vacca A; Ribatti D; Presta M
TI Basic fibroblast growth factor overexpression in endothelial cells: an autocrine mechanism for angiogenesis and angioproliferative diseases.
SO Cell growth & differentiation : molecular biology journal of the American Association for Cancer Research, (1996 Feb) 7 (2) 147-60.
Journal code: 9100024. ISSN: 1044-9523.
AB Basic fibroblast growth factor (bFGF) is expressed in vascular endothelium during tumor neovascularization and angioproliferative diseases. The ultimate significance of this observation is poorly understood. We have investigated the biological consequences of endothelial cell activation by endogenous bFGF in a mouse aortic endothelial cell line stably **transfected** with a retroviral expression vector harboring a human bFGF cDNA. Selected clones expressing M(r) 24,000, M(r) 22,000, and/or M(r) 18,000 bFGF isoforms were characterized by a **transformed** morphology and an increased saturation density. bFGF **transfectants** showed invasive behavior and sprouting activity in three-dimensional **fibrin gels** and formed a complex network of branching cord-like structures connecting foci of infiltrating cells when seeded on laminin-rich basement membrane matrix (Matrigel). The invasive and morphogenetic behavior was prevented by anti-bFGF antibody, revealing the autocrine modality of the process. The biological consequences of this autocrine activation were investigated in vivo. bFGF-**transfected** cells gave rise to highly vascularized lesions resembling Kaposi's sarcoma when injected in nude mice and induced angiogenesis in avascular rabbit cornea. When injected into the allantoic sac of the chick embryo, they caused an increase in vascular density and formation of hemangiomas in the chorioallantoic membrane. In conclusion, bFGF-overexpressing endothelial cells acquired an angiogenic phenotype and recruit quiescent endothelium originating angioproliferative lesions in vivo. These findings demonstrate that bFGF overexpression exerts an autocrine role for endothelial cells and support the notion that tumor neovascularization and angioproliferative diseases can be triggered by stimuli that induce vascular endothelium to produce its own autocrine factor(s).

L6 ANSWER 12 OF 13 MEDLINE on STN DUPLICATE 3
AU Katagiri Y; Hiroyama T; Akamatsu N; Suzuki H; Yamazaki H; Tanoue K
TI Involvement of alpha v beta 3 integrin in mediating **fibrin gel** retraction.
SO Journal of biological chemistry, (1995 Jan 27) 270 (4) 1785-90.
Journal code: 2985121R. ISSN: 0021-9258.

AB Platelet integrin alpha IIb beta 3 (GPIIb-IIIa) plays important roles in platelet-mediated clot retraction. However, little is known about the mechanisms of clot retraction mediated by nucleated cells. In this report, we demonstrate that another member of the beta 3 integrin family, alpha v beta 3, is involved in clot retraction mediated by nucleated cells. Retraction of fibrin clots was observed using a human melanoma cell line, C32TG, which contains no alpha IIb beta 3 complex. This retraction was inhibited by RGD-containing peptide, monoclonal anti-beta 3, and anti-alpha v beta 3 antibodies. Immunoelectron microscopic studies revealed a direct interaction between beta 3 integrin and fibrin fibers at an early stage of clot retraction. We found that another human embryonal cell line, 293, which is known to express alpha v beta 1, but no alpha v beta 3, lacks **fibrin gel** retractile activity. Upon **transfection** of beta 3 **DNA** into 293 cells, the beta 3 subunit formed a complex with an endogenous alpha v subunit. The beta 3-bearing **transfectants** were found to retract **fibrin gels**, which was specifically inhibited by anti-beta 3 antibody. In addition, a point mutation at Asp119 in the beta 3 ligand binding domain abolished the clot retractile activity of 293 **transfectants**, indicating the requirement of alpha v beta 3 ligand-binding activity. Our findings suggest that alpha v beta 3 is involved in mediating the interaction between the three-dimensional fibrin network and nucleated cells and in promoting "post-receptor occupancy" events.

L6 ANSWER 13 OF 13 MEDLINE on STN
AU Pepper M S; Belin D; Montesano R; Orci L; Vassalli J D
TI **Transforming** growth factor-beta 1 modulates basic fibroblast growth factor-induced proteolytic and angiogenic properties of endothelial cells in vitro.
SO Journal of cell biology, (1990 Aug) 111 (2) 743-55.
Journal code: 0375356. ISSN: 0021-9525.
AB Tightly controlled proteolytic degradation of the extracellular matrix by invading microvascular endothelial cells is believed to be a necessary component of the angiogenic process. We have previously demonstrated the induction of plasminogen activators (PAs) in bovine microvascular endothelial (BME) cells by three agents that induce angiogenesis in vitro: basic FGF (bFGF), PMA, and sodium orthovanadate. Surprisingly, we find that these agents also induce plasminogen activator inhibitor-1 (PAI-1) activity and mRNA in BME cells. We also find that **transforming** growth factor-beta 1 (TGF-beta 1), which in vitro modulates a number of endothelial cell functions relevant to angiogenesis, also increases both PAI-1 and urokinase-type PA (u-PA) mRNA. Thus, production of both proteases and protease inhibitors is increased by angiogenic agents and TGF-beta 1. However, the kinetics and amplitude of PAI-1 and u-PA mRNA induction by these agents are strikingly different. We have used the ratio of u-PA:PAI-1 mRNA levels as an indicator of proteolytic balance. This ratio is tilted towards enhanced proteolysis in response to bFGF, towards antiproteolysis in response to TGF-beta 1, and is similar to that in untreated cultures when the two agents are added simultaneously. Using an in vitro angiogenesis assay in three-dimensional **fibrin gels**, we find that TGF-beta 1 inhibits the bFGF-induced formation of tube-like structures, resulting in the formation of solid endothelial cell cords within the superficial parts of the gel. These results suggest that a net positive proteolytic balance is required for capillary lumen formation. A novel perspective is provided on the relationship between extracellular matrix invasion, lumen formation, and net proteolytic balance, thereby reflecting the interplay between angiogenesis-modulating cytokines such as bFGF and TGF-beta 1.

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